REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 16-18, 22-26, 30-34 and 36, as well as newly added Claims 39-56, the only claims pending and currently under examination in this application following entry of the above requested amendments.

Claims 16 and 30 have been amended to exactly match the wording of the specification at page 5, line 12, regarding the molecular weight of the bifunctional molecules. New dependent claims 39-56 have been introduced. These claims find full support in the specification at page 21, lines 13ff. No new matter has been introduced to the application by the above amendments. As such, the Examiner is respectfully requested to enter the above amendments.

ENABLEMENT

Claims 16-18, 22-26, 30-34 and 36 have been rejected under 35 U.S.C. § 112, 1st ¶ for an asserted lack of enablement. In making this rejection, the Examiner cites to the *In re Wands* factors, and asserts that, in view of the following four factors:

1) scope of claims

2) amount of guidance provided

3) lack of sufficient working examples; and

4) unpredictability of field;

it would require undue amount of experimentation on the part of one skilled in the art to practice the full scope of the claimed invention.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the

disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims. [2]

By applying these eight factors to the present application, the Applicants respectfully submit that the specification, coupled with the information known in the art, would enable one of skill in the art to practice the full scope of the claimed invention without undue experimentation.

(A & B) THE QUANTITY OF NECESSARY EXPERIMENTATION AND THE AMOUNT OF GUIDANCE PROVIDED

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP § 2164.01.[3]

As the *Wands* court explained:

> a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.[4]

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[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

[2] *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

[3] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

[4] *In re Wands* 8 USPQ 2d at 1404.

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.

Turning to the present application, the bifunctional molecules employed in the subject methods are extensively described in the specification beginning at page 4 of the specification. This includes a generic description of these molecules, a detailed description of these molecules in terms of formulas, an extensive description of each of the component parts of the molecules, e.g., drug moieties (see pages 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23).

In addition, a detailed description of how to make the targeted bifunctional molecules is provided at pages 24 to 28 of the specification, where specific guidance is provided on how to make the compounds. Three representative methods of making the compounds are described. Furthermore, page 26 provides even more detail regarding bifunctional molecules of the invention that include a peptidyl-prolyl isomerase-targeting moiety.

Guidance on how to screen candidate bifunctional molecules for suitability of use in the claimed methods is provided on page 25.

Finally, page 29 of the specification provides an extensive description on how to use the bifunctional molecules in various applications, including dosages and administration routes, types of hosts, types of conditions, etc.

In view of the above, it is clear that the specification has provided sufficient

guidance and description for one of skill in the art to make and use the claimed invention without undue experimentation. As such, the amount of experimentation necessary is not undue in view of the guidance provided by the specification. Though time-consuming, it is well within the skill of the ordinary practitioner to obtain a drug moiety and a targeting moiety as claimed, and to link them to form a bifunctional molecule (with or without a linker moiety) as taught in the specification, using well known methods of synthetic organic chemistry. The bifunctional molecules which are most suitable for use in the claimed methods can be identified using well known screening techniques described in the specification, with some experimentation, and with a reasonable expectation of success. In this field, a person of ordinary skill in the art would not consider the experimentation to be undue, because the synthesis and evaluation of large numbers of compounds is expected and routine in the pharmaceutical arts.

(C) THE PRESENCE OR ABSENCE OF WORKING EXAMPLES

Compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed, nor that examples be "working" examples. No more is needed than that the invention be disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation. Furthermore, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples." In view of the above described extensive guidance provided by the specification in the present application, it is respectfully submitted that the present application does enable a person skilled in the art to apply the teachings in the specification in conjunction with the relevant art to make and use the full scope of claimed invention.

Furthermore, specific representative examples are provided. Embodiments of the claimed bifunctional molecules having a drug moiety bound to FK506 or rapamycin are provided in the Experimental section of the specification, beginning at page 33. In this exemplary embodiment the drug moiety and FK506 or rapamycin targeting moiety are

connected by an inert linking group. The resulting bifunctional molecules are suitable for "targeting to the intracellular space" as claimed. Specification, p. 33. Specific drug moieties in the bifunctional molecules, for targeting specific types of cells, are also exemplified. *See*, specification at 33-34 (melanoma, liver, and microbial cells). Targeting moieties which bind to endogenous peptidyl-prolyl isomerase modulating proteins are also exemplified, such as FKBPs and cyclosphilins, and FK506 is further described as a representative targeting moiety. Specification, at 26-28.

Further embodiments in the nature of "working examples" are not required. These examples, together with the rest of the specification, and given the knowledge in the art at the time of the invention, are sufficient to provide an enabling disclosure.

(D, E & F) NATURE OF THE INVENTION; THE STATE OF THE PRIOR ART; THE RELATIVE SKILL OF THOSE IN THE ART

The invention is in the fields of synthetic organic chemistry, pharmacology and biotechnology. More specifically, the claimed invention is directed to engineered bifunctional molecules for directing a drug to an intracellular space. The bifunctional molecules have potential therapeutic uses, among other applications. The relevant fields are advanced and mature, such that the methods of making and using the described bifunctional molecules according to the claimed methods would require the use of routine synthesis and screening protocols described in the specification and well known to those of skill in the art. Furthermore, the relevant ordinarily skilled artisan is generally a scientist with a doctoral degree in chemistry, pharmacology or biotechnology techniques, or equivalent experience.

(G) THE PREDICTABILITY OR UNPREDICTABILITY OF THE ART

It is respectfully submitted that the relevant field of the invention is not so unpredictable, as asserted by the Examiner. Specifically, it is submitted that, using the guidance provided in the specification and the knowledge of those of ordinary skill in the art, one could make bifunctional drugs of the multitude of drugs listed on pages 6 to 16

of the specification, by using conventional chemistry linking protocols, such as the representative protocols provided in the specification. Accordingly, it is predictable that one could successfully make bifunctional molecules of the multitude of drugs provided in the specification, e.g., by linking the drugs directly to a targeting moiety or by using a linker disclosed in the specification. It is also predictable that routine testing, including well known screening methods, will successfully identify those bifunctional molecules which target the intracellular space compared to a free drug control. Although experimentation is needed, and all experimentation is somewhat uncertain, the amount of experimentation is ordinary and expected in this field, and *success* is reasonably predictable. See e.g., In re Geerdes, 180 U.S. P.Q. 789 (CCPA, 1974).

(H) THE BREADTH OF THE CLAIMS

The Examiner asserts that the breadth of the claims includes the administration of a genus of bifunctional molecules, which is considered unduly large. However, in view of the extensive guidance of the specification, the advanced nature of the field, the high level of skill of those in the art, and the predictability of success in being able to make and use the bifunctional molecules as claimed, it is submitted that the scope of the claims is fully enabled by the specification.

As explained above, a person of ordinary skill in the art, from the specification, would be able to link a known drug to a targeting moiety, including those exemplified in the disclosure, in order to improve bio-distribution to an intracellular space compared to the drug alone, with reasonable experimentation and reasonable expectation of success.

In view of the above, it is respectfully submitted that Claims 16-18, 22-26, 30-34 and 36 are fully enabled under 35 U.S.C. § 112, 1st ¶ and that this rejection may be withdrawn.

WRITTEN DESCRIPTION

Claims 16-18, 22-26, 30-34 and 36 have been rejected under 35 U.S.C. § 112, 1st ¶ for assertedly failing to comply with the written description requirement.

However, the bifunctional molecules employed in the subject methods are extensively described in the specification beginning at page 4 of the specification. This extensive description includes a generic description of these molecules, a description of these molecules in terms of formulas, an extensive description of each of the component parts of the molecules, e.g., drug moieties (see pages 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23) as well as a detailed description of how to make these targeted bifunctional molecules (see pages 24 to 28). Furthermore, the specification provides extensive discussion of how to screen bifunctional molecules for desirable activity, and how to use, them for various applications, (including details on dosages, dosage forms and routes of delivery). As such, the bifunctional molecules are fully described in the specification both in terms of component parts, how to make them, and the resulting bifunctional molecules. The bifunctional molecules are described in structural terms, as well as in terms of functional characteristics arising from those structures – particularly the component parts and how they are linked. One of skill in the art would read the specification and know that the Applicants were in possession of the invention as claimed: a generic method for directing a drug to an intracellular space by linking the drug to a targeting moiety, compared to the drug alone.

It is noted that the Examiner's position is apparently premised on the erroneous belief that no additional species beyond the representative FK506, cyclosporin or rapamycin species are described in the specification. See top of page 7 of the Office Action. However, in the Experimental section, additional representative species are disclosed, including chloroquine-containing bifunctional molecules for targeting drugs to melanoma cells (page 34) and quinacrine-containing bifunctional molecules for targeting liver cells (page 34). Accordingly, additional species are disclosed.. The Applicants

submit that the representative examples are sufficient in kind and number to support the claims.

In view of the above, it is respectfully submitted that the specification demonstrates that the Applicants were in possession of the claimed invention at the time the application was filed. Accordingly, Claims 16-18, 22-26, 30-34 and 36 comply with the written description requirement of 35 U.S.C. § 112, 1st ¶ and this rejection may be withdrawn.

LESS THAN ABOUT 5000 DALTONS

Claims 16-18, 22-23, 30-34 and 36 have been rejected under 35 U.S.C. § 112, 1st ¶ for an asserted lack of support for the phrase "bifunctional molecule of less than about 5000 daltons" appearing in Claims 16 and 30. In view of the above amendments to Claims 16 and 30, this rejection may be withdrawn.

Claim 32 has been rejected under 35 U.S.C. § 112, 2nd ¶. In view of the above amendment to Claim 32, this rejection may be withdrawn.

To advance prosecution, and although the Applicants believe the original claim language "less than about 5000 daltons" is adequately supported, the claims have been amended to recite "does not exceed about 5000 daltons." This language is supported exactly by the specification, page 5 lines 12. Accordingly, the rejection may be withdrawn.

OBVIOUSNESS

Finally, Claims 16-18, 22-26, 30-34 and 36 have been rejected under 35 U.S.C. § 103(a) as being obvious over Pichon in view of U.S. Patent No. 5,830,462 and WO 95/10302.

An element of all of the pending claims is that the bifunctional molecule is directed to an intracellular site of a host by the targeting moiety. Pichon teaches that ODN-KDEL or -KDEA peptides were internalized 4-fold less than the corresponding peptide free ODNs. As such, Pichon teaches that delivering the ODN "drug" as a bifunctional molecule with a peptide targeting moiety actually resulted in worse internalization of the ODN drug as compared to the ODN drug by itself. Accordingly, Pichon teaches that if one wants to direct a drug to an intracellular site, one should not administer the drug as a bifunctional molecule because doing so results in reduced internalization as compared to a free drug control. **Therefore, Pichon actually teaches away from the claims of the present invention.**

Furthermore, the rejection is based in part on the Examiner's assumption that it would be obvious to substitute the ODN drug moiety of Pichon for the FK506 or cyclosporin "drug moieties" of U.S. Patent No. 5,830,462, as further suggested by WO 95/10302. See Page 11 of the office action.

However, these references fail to overcome the teaching-away by Pichon, which actually shows that in general one should not administer a drug as a bifunctional molecule with a targeting moiety where the goal is to direct the drug to an intracellular space, since to do so would result in lower internalization. It follows that there would have been no motivation to modify Pinchon to improve the biodistribution of a drug to an intracellular space. There would be no suggestion, and no motivation, to replace ODN with FK506 or any other targeting moiety from the secondary references.

Furthermore, in the Examiner's rejection, the FK506 and cyclosporine are identified as “drug moieties” which would replace the ODN drug moiety of Pinchon. As such, the Examiner asserts that what is obvious in view of the combined teaching of the references is an FK506 or Cyclosporine drug moiety conjugated to KDEL targeting moiety.

This approach appears to confuse the drug moeites and targeting moieties of the

claimed invention of the present application with the very different teachings of the references. Specifically, in the present invention the FK506 or cyclosporine moieties are targeting moieties, **not drug moieties**. Accordingly, if one were to substitute the FK506 or cyclosporine moieties of the supplemental references for the ODN moiety of Pinchon's bifunctional molecule, one would still not arrive at the claimed invention, because one would have produced a bifunctional molecule with two "targeting" moieties and no drug moieties.

In fact, Pinchon compares ODN alone with ODN-KDEL, indicating that, if anything, the KDEL should be substituted by other moieties to reduce internalization. This would not have led to an ODN-FK506 bifunctional molecule, nor any other bifunctional molecule, and certainly not to one that would increase internalization.

Finally, the Examiner again relies in part on the teachings of Briesewitz et al. Office Action, p. 11. As already demonstrated in the Applicants' previous response, Briesewitz et al. does not qualify as prior art to the present application. Accordingly, this rejection is improper and should be withdrawn.

In view of the above remarks, it is respectfully submitted that Claims 16-18, 22-26, 30-34 and 36 are not obvious under 35 U.S.C. § 103(a) over Pichon in view of U.S. Patent No. 5,830,462 and WO 95/10302 and this rejection may be withdrawn.

CONCLUSION

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

Date: 6·3·04

By: _____

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